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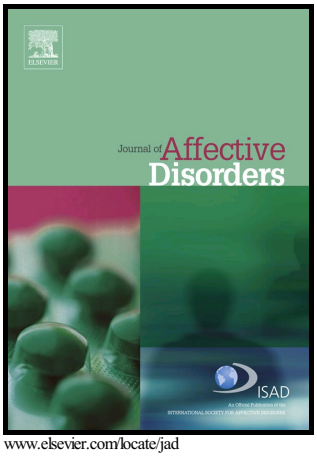

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Association between vitamin D and depressive symptoms varies by season: results from the German Health Interview and Examination Survey for Adults (DEGS1)

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Abbreviations

25(OH)D - 25-hydroxy-vitamin-D; BMI - Body Mass Index ; CES-D - Center for Epidemiologic Studies Depression; CKD-EPI - The Chronic Kidney Disease Epidemiology Collaboration ; DEGS1 - The German Health Interview and Examination Survey for Adults ; DSM-IV - Diagnostic and Statistical Manual of Mental Disorders IV ; eGFR - estimated glomerular filtration rate ; GDS - Geriatric Depression Scale; PF - Physical functioning;

PHQ-9 - 9-item depression module of the Patient Health Questionnaire ; SCL-10 - Hopkins Symptoms Check List 10 ; SES - Socio-economic status ; SF-36 - Short Form-36 Health Survey; UVB - ultraviolet B

Abstract

Background

Findings from epidemiological studies regarding seasonal variations in the association between vitamin D status and depression are inconsistent.

Methods

Cross-sectional analysis of data from 6,331 participants aged 18-79 years in the nationwide representative German Health Interview and Examination Survey for Adults 2008-2011 (DEGS1). Associations between 25-hydroxy-vitamin-D (25(OH)D) serum levels in quartiles and current depressive symptoms as measured by the Patient Health Questionnaire depression module (PHQ-9) and defined as severity of depressive symptoms (PHQ-9 score, range 0-27 points) and elevated depressive symptoms (PHQ-9 score >= 10 points) were analysed using multivariable linear and logistic regression adjusted for sociodemographic, biological and lifestyle factors. Analyses were stratified by summertime (May to October) and wintertime (November to April) because of evidence for interaction with season (p=<0.01).

Results

In crude analyses, vitamin D status was inversely associated with both depression outcomes in summertime but not in wintertime. After adjustment for potential confounders, a significant association with severity of depressive symptoms remained in summer, with 0.73 point lower PHQ-9 scores in the highest versus lowest quartile. The association between 25(OH)D quartiles and elevated depressive symptoms in summertime was less strong and no longer significant in fully adjusted models.

Limitations

Participants with severe depression may be underrepresented in DEGS1. Residual confounding cannot be excluded.

Conclusion

25(OH)D serum levels were inversely associated with current depressive symptoms in summer but not in wintertime. The fact that the association is stronger in summertime suggests that vitamin D deficiency may be a consequence rather than a cause of depression.

1. Introduction

Depression is a highly prevalent mental disorder and an important public health issue worldwide. It is one of the leading contributors to the global burden of disease, a major cause of disability (Ferrari et al., 2013) and associated with increased mortality and high healthcare costs (Cuijpers and Smit, 2002; Sobocki et al., 2006; Zheng et al., 1997).

The etiology of depression is not completely established. Besides psychosocial factors, different biological and environmental factors are considered to play a potential role in its pathophysiology (Saveanu and Nemeroff, 2012). Increasingly, vitamin D deficiency is being suggested as a contributor to depression (Ju et al., 2013; Milaneschi et al., 2014). The presence of vitamin D receptors and vitamin D-activating enzymes in several parts of the human brain known to contribute to the regulation of mood like the hippocampus, hypothalamus and prefrontal cortex provide plausible biological explanations for the relationship between vitamin D deficiency and low mood (Eyles et al., 2005). In addition, there is evidence that vitamin D is a potent inducer of nerve growth factor synthesis (Brown et al., 2003; Wion et al., 1991) and is involved in the expression of monoamines, such as norepinephrine and serotonin, which are associated with depression (Cass et al., 2006; Garcion et al., 2002; Smith et al., 2006).

Depressive symptoms are common during winter among countries in northern latitudes when vitamin D levels may be lower due to inadequate ultraviolet B (UVB) radiation resulting in decreased vitamin D synthesis in the skin (Engelsen et al., 2005; Tsiaras and Weinstock, 2011). Remarkably, relatively few studies have examined the influence of season on the association between vitamin D and depression (Brandenbarg et al., 2012; Hoang et al., 2011; Kjaergaard et al., 2011; Nanri et al., 2009; Stewart and Hirani, 2010). Results from these studies were mixed; three studies did not observe an influence of season (Brandenbarg et al., 2012; Nanri et al., 2009; Stewart and Hirani, 2010), while the other two studies reported conflicting evidence for an inverse association between vitamin D and depressive symptoms in winter (Hoang et al., 2011) and in summer (Kjaergaard et al., 2011).

In this study, we examined the association between 25(OH)D serum levels and current depressive symptoms by season in a nationally representative sample of adults in Germany; a

northern European country with well-defined seasons and a latitudinal position between 47°-55°N where vitamin D skin sythesis is limited between October and March (Rabenberg et al., 2015) .

2. Methods

2.1 Study design and subjects

The 'German Health Interview and Examination Survey for Adults' (DEGS1) was conducted between November 2008 and December 2011 and included a nationwide representative population-based sample of adults aged 18–79 years in Germany. The design and methods of DEGS1 have been described in detail elsewhere (Kamtsiuris et al., 2013; Rabenberg et al., 2015; Scheidt-Nave et al., 2012). Briefly, participants were selected using a two-stage stratified random sampling procedure from local population registries at 180 selected sample points across Germany. The sequence of places visited by two mobile study teams was laid down in advance in a random touring schedule, in order to avoid a systematic bias of study results by seasonal or time trends or municipality size (Gosswald et al., 2013).

In total, 7,987 persons aged 18-79 years took part in DEGS1 and of these, 7,115 participants had a wide range of examinations and blood tests in addition to a physician-administered personal interview and a self-administered questionnaire.

For this study, participants with missing data on serum levels of 25-hydroxy-vitamin-D (25(OH)D) (n=120), depressive symptoms (n=369) or relevant covariables (n=295) were excluded, resulting in a study population of 6,331 persons (3,290 women; 3,041 men).

DEGS1 was developed in line with the principles of the Declaration of Helsinki and was approved by the Federal and State Commissioners for Data Protection and by the ethics

committee of the Charité-Universitätsmedizin Berlin (No. EA2/047/08). Written informed consent was obtained from participants.

2.2 Data collection and measures

2.2.1 Depressive symptoms

Presence and frequency of depressive symptoms in the two weeks prior to interview was assessed with the German version of the 9-item depression module of the Patient Health Questionnaire (PHQ-9) (Busch et al., 2013; Kroenke et al., 2001). The items of this written, self-administered questionnaire are based on the nine diagnostic criteria for major depression of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) including depressed mood, decreased interest or pleasure in activities, significant weight change or change in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, problems with concentration, and suicidal thoughts (American Psychiatric Association, 2013). The frequency of each diagnostic criterion is rated as 0 (“not at all”), 1 (“several days”), 2 (“more than half the days”) or 3 (“nearly every day”). Individual item scores are summed to produce a PHQ-9 total score, ranging from 0 to 27. Persons with scores of >=10 are categorized as having elevated depressive symptoms (Kroenke et al., 2001).

In the present study, the PHQ-9 score was analysed as both a continuous variable (range 0-27) for severity of depressive symptoms and as a dichotomous variable using the cut-point case definition (PHQ-9 score >=10) for elevated depressive symptoms.

2.2.2 Vitamin D status

Venous blood samples were drawn at study assessement centres and immediately centrifuged and separated. Serum samples were aliquoted and stored at −40°C. Samples were transported and analysed at the central epidemiology laboratory unit at the Robert Koch Institute, Berlin. Measurement of serum 25(OH)D was carried out using a Liaison chemiluminescence immunoassay (DiaSorin Inc., Stillwater, MN, USA). Full details on analyses have been described elsewhere (Rabenberg et al., 2015). When measured serum 25(OH)D values were below 10 nmol/l, the lower detection level of the assay, values were set to 9 nmol/l. This was the case for 111 participants. For all analyses, serum 25(OH)D quartiles were used.

2.2.3 Covariables

Socio-demographic, biological and lifestyle factors which are known to be associated with depressive symptoms and vitamin D status were taken into account as potential confounders. Extended season was defined by the month of examination and categorised as summertime (May-October) in which UVB exposure is more likely to be adequate for vitamin D skin synthesis and wintertime (November-April) (Rabenberg et al., 2015).

Socio-economic status (SES) was defined using information on education, occupation, and household income and was categorized as low, middle and high (Lampert et al., 2013). Living arrangements and marital status were assessed by a self-administered questionnaire and dichotomized into living in a partnership (including married persons) versus not living in a partnership (separated, divorced, widowed or single). Municipality size was classified as rural (<5,000 inhabitants), small town (5,000 to <20,000 inhabitants), medium-sized town (20,000 to <100,000 inhabitants) and large town (≥100,000 inhabitants) (Kamtsiuris et al., 2013).

As skin pigmentation and cultural dress codes (e.g. veiling) are known to influence vitamin D skin synthesis (Palacios and Gonzalez, 2014), we attempted to consider these factors using

country of birth of participants in the analysis. Drawing on a previous study investigating vitamin D deficiency and immigration background in Germany (Hintzpeter et al., 2008), we grouped country of birth into 'Germany', 'Europe and Western countries' (including USA, Canada, Europe and the former Soviet Union), 'Arab-Islamic countries' (including Turkey, the largest immigrant group in Germany) and 'remaining countries' (including Latin America, Asia and Africa).

Body weight and height were measured with standardized measurements with participants wearing underwear only. Body Mass Index (BMI) was calculated as weight (in kg)/(height (in m))^2 and categorized as obese (BMI >=30) or non-obese (BMI <30) according to World Health Organization recommendations (World Health Organization, 2000). Physical function was assessed by the 10-item physical functioning (PF) subscale of the Short Form-36 Health Survey (SF-36) (Jenkinson et al., 1999; Ware, 2000). Established methods were used to calculate PF scores ranging from 0 to 100, with higher scores indicating better physical functioning (Ware et al., 2007). Kidney function was assessed by the estimated glomerular filtration rate (eGFR) based on serum creatinine level and using the equation from 'The Chronic Kidney Disease Epidemiology Collaboration' (CKD-EPI) (Levey et al., 2009): eGFR = 141 x $\min(S_{Cr}/\kappa, 1)^{\alpha}$ x $\max(S_{Cr}/\kappa, 1)^{-1.209}$ x 0.993^{Age} x 1.018 [if female]. S_{Cr} stands for standardized serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{Cr}/κ or 1, and max indicates the maximum of S_{Cr}/κ or 1. An eGFR value of 90 mL/min/1.73 m^2 or higher designates a normal level in most healthy people.

Smoking status was classified as current smoking (even occasionally) or no current smoking (including former and never smoking). Volume and frequency of alcohol consumption was grouped into the categories 'no consumption', 'alcohol consumption with <10 g/day for

women and <20 g/day for men' and 'alcohol consumption with >=10 g/day for women and >=20 g/day for men' according to tolerable maximum intake per day from the German Nutrition Society (Deutsche Gesellschaft für Ernährung e.V. et al., 2015). Sports activity in the last three months was assessed by the question 'How often do you participate in sports during one week?'(Krug et al., 2013). The response options 'I don't do any sports', 'less than 1 hour', 'regularly 1 to 2 hours', 'regularly 2 to 4 hours' and 'regularly more than 4 hours' were dichotomized into 'no sport activity/week' and 'sport activity >0 hour/week'.

2.3 Statistical Analyses

Prevalences and means of sample characteristics were calculated according to 25(OH)D quartiles and elevated depressive symptoms (PHQ-9 >= 10). Associations between sample characteristics and 25(OH)D quartiles and elevated depressive symptoms were tested using the chi-square test for categorical variables and linear regression for continuous variables.
In preliminary analyses, we tested for interaction between 25(OH)D quartiles and sex, age group and extended season by adding multiplicative interaction terms to linear and logistic regression models that included these variables (data not shown). While there was no evidence for an interaction with age group or sex, an interaction with extended season was seen for both depressive symptoms variables (p=<0.01). Thus, all analyses were stratified by summertime and wintertime.

To examine associations between 25(OH)D quartiles and depressive symptoms, we first calculated mean PHQ-9 scores and prevalences of elevated depressive symptoms year-round and then stratified these by summer and wintertime. We initially tested for trends across serum 25(OH)D quartiles using unadjusted linear and logistic regression analyses.

We then performed multivariable analyses stratified by summer and wintertime. We used multivariable linear regression when severity of depressive symtoms (PHQ-9 score) was the dependent variable and logistic regression when elevated depressive symptoms (PHQ-9 >=10) was the dependent variable. Multivariable regression models were adjusted for: sex, age, SES, living arrangements (living in a partnership), municipality size, country of birth, obesity, physical functioning, kidney function (eGFR), smoking status, alcohol consumption and sports activity.

All analyses were calculated using a weighting factor which accounts for the sampling design and corrects sample deviations from the German population structure (as on 31. December 2010) with regard to age group, sex, region, nationality, type of municipality and education. To take into account both the weighting factor and the correlation of participants within communities, all analyses were performed with complex samples procedures in SPSS version 20.0 (SPSS Inc.,Chicago, Illinois, USA). For all analyses, a p-value <0.05 based on two-sided tests was considered statistically significant.

3. Results

The mean age of the sample was 46.8 (95% CI 46.3-47.3) years and mean value of serum 25(OH)D was 46.2 nmol/l (95% CI 44.1-48.3) with no significant differences between women and men (46.7 nmol/l vs. 45.7 nmol/l; p-value = 0.28). The mean value of PHQ-9 score was 4.1 (95% CI 3.9-4.2) and 7.5 % had elevated depressive symptoms (PHQ-9 >=10). Table 1 summarizes the characteristics of the study population across serum 25(OH)D quartiles and for persons with and without elevated depressive symptoms. Participants in the highest vitamin D quartile were more likely to be younger. For example, the proportion of participants in the age group 18 to 29 years increased from 19.8% in the lowest quartile to

24.3% in the highest quartile, with p<0.001 for difference in all age groups across quartiles. The proportion of participants examined in summertime rose from 19.1% in the lowest to 72.9% in the highest quartile (p<0.001). Participants in the highest quartiles were also more likely to have higher SES, to live in a partnership, to live in large towns, to be of German origin, to not be obese, to have higher physical functioning, to drink less alcohol and to regularly participate in sport.

Having elevated depressive symptoms was associated with being female, belonging to younger age groups, lower SES, not living in a partnership, living in larger towns, not being of German origin, obesity, lower physical functioning, current smoking and not participating in sports activities.

Characteristics of participants, however, did not differ by half year (data not shown).

Table 2 shows the severity of depressive symptoms (mean PHQ-9 score) and the prevalence of elevated depressive symptoms (PHQ-9 >=10) according to serum 25(OH)D quartiles year-round and by summer and wintertime. Increasing vitamin D serum concentration was significantly associated with lower severity of depressive symptoms, year-round and in summertime, but not wintertime. In relation to elevated depressive symptoms, there was a significant association with vitamin D status only in summertime.

Table 3 and 4 present the results of the multivariable regression analyses. There was a consistent significant association with mean PHQ-9 scores in summertime, but not wintertime, across all multivariable linear regression models (Table 3). In the fully adjusted linear model (Model 4), there was a 0.73 lower PHQ-9 score in the highest versus the lowest quartile. However, the association between serum 25(OH)D quartiles and the prevalence of elevated depressive symptoms (PHQ-9 >=10) in the logistic regression analyses was no longer significant after adjusting for biological factors and health behaviour (Table 4). In the

wintertime, there was no consistent association between vitamin D status and mean PHQ-9 scores (Table 3) or elevated depressive symptoms (Table 4) .

4. Discussion

In this large nationwide representative study of the population aged 18–79 years in Germany, we found an inverse association between serum 25(OH)D levels and current depressive symptoms in summertime, but not wintertime.

Our study examined two aspects of current depressive symptoms as outcomes; the severity of symptoms using a PHQ-9 as a continous variable and a cut-point based case definition of elevated depressive symptoms. Interestingly, we found significant associations persisted in the final linear regression model, but not in the logistic regression analysis using a case definition of depressive symptoms as the outcome. These differences highlight how different methodological approaches influence results and the need for specificity in reporting. Associations between depressive symptoms and vitamin D status in the linear models show that although the association is present in summertime, relationships between clinical thresholds for depressive symptoms and vitamin D status may be under greater influence of other biological and lifestyle factors than the season.

In the last decade, several studies examined the association between vitamin D and depression (Ganji et al., 2010; Hoogendijk et al., 2008; Lee et al., 2011; Milaneschi et al., 2010; Polak et al., 2014; Williams et al., 2014). Findings have been inconsistent, with some studies reporting a relationship (Ganji et al., 2010; Hoogendijk et al., 2008; Lee et al., 2011; Milaneschi et al., 2010; Polak et al., 2014; Williams et al., 2014) and others finding no relationship (Almeida et al., 2015; Pan et al., 2009; Zhao et al., 2010). Although depressive symptoms are common during winter times in northern latitudes, only a few studies specifically examined the

influence of season on the association (Brandenbarg et al., 2012; Hoang et al., 2011; Kjaergaard et al., 2011; Nanri et al., 2009; Stewart and Hirani, 2010).

Our findings are consistent with results reported from the 'Tromsø Study' in Norway, a longitudinal, population-based study which measured vitamin D status and depressive symptoms (defined as a score >=1.85 on Hopkins Symptoms Check List 10 (SCL-10)) in 10,086 persons aged 30 to 87 years (Kjaergaard et al., 2011). In this north Norwegian study, logistic regression analyses stratified by half year and smoking status showed that in the summertime serum 25(OH)D was a significant predictor of the SCL-10 score in females in the non-smoking group (p=0.020) and in males in the smoking group (p=0.035). Nevertheless, effect modification by season was not statistically tested.

Contrary to our findings are those from a cross-sectional study of 12,594 people aged 20 to 90 years attending a preventive medicine clinic in Texas, in the US. In this study, an inverse association between vitamin D levels and current depressive symptoms (defined as 10-item Center for Epidemiologic Studies Depression (CES-D) scale score of >=10) was observed for wintertime (October to March) (OR=0.87 (0.80-0.95); p=0.001) but not summertime (April to September) (OR= 0.96 (0.89-1.02); p=0.2) (Hoang et al., 2011). However, interaction testing between season and vitamin D level was not reported in this US study and confidence intervals of effect estimates overlapped widely, limiting any inference to effect modification by season. Nevertheless, overall vitamin D levels were comparatively high in this study and no difference in absolute vitamin D levels were found between seasons. Importantly, even between October to March, the number of months with adequate UVB exposition in this region is much higher than in Germany and Norway and may explain our different findings.

Three other studies investigating the influence of season on the association between vitamin D status and depression have failed to find any associations. In a study using data from the

Health Survey for England 2005 (Stewart and Hirani, 2010), including 2,070 participants aged >=65 years, depressive symptoms (defined using a Geriatric Depression Scale (GDS10) score >=3) were associated with vitamin D levels <25 nmol/l in the overall sample but without effect modification by season (interaction term: p=0.84) in an analysis adjusted for age, sex and social class. Similar results were reported from the 'Amsterdam Born Children and Their Development cohort', which measured vitamin D status and depressive symptoms (defined as a score >=16 on the 20-item CES-D scale) in 4,101 pregnant women with mean age of 31 years (Brandenbarg et al., 2012). Analyses showed an inverse association between vitamin D concentrations and levels of depressive symptoms but no effect modification by season (interaction term: p=0.39). Similarly, although using different methods, a study of 527 office workers in Japan aged 21 to 67 years (Nanri et al., 2009) found no significant association between vitamin D status and depressive symptoms (CES-D score of >= 16) or severe depressive symptoms (CES-D score of >= 23) between two groups of workers examined in different seasons (July and November).

Conflicting results found across previous studies are likely to be underpinned by diverse study methodology. Several differences including the observed population and age groups, definitions of seasons, heterogenity in instruments used to assess depressive symptoms, and various methods to analyse vitamin D and cut-offs to determine depression and vitamin D deficiency make direct comparisons with previous studies challenging. Moreover, studies accounted for different confounders which is likely to contribute to these incongruent findings.

Although many cross-sectional and longitudinal studies observed an inverse association between vitamin D and depressive symptoms, the direction of causation remains unclear. Regarding, for example, the effects of vitamin D on nerve growth factor synthesis or

neurotransmitter like serotonin, lower levels may contribute to depression (Brown et al., 2003; Cass et al., 2006; Garcion et al., 2002; Smith et al., 2006; Wion et al., 1991). On the other hand, vitamin D deficiency may also be a consequence of depression. Depressed persons are more likely to stay inside and, thus, less exposed to sunlight. While this is less important during fall and winter because the endogenous vitamin D production is limited in northern latitudes (above latitude 35° North), and outside activity does not have an impact on vitamin D level, it is of more consequence in the summer half year when vitamin D synthesis is possible. Following this reasoning, the results of this study tend to support the hypothesis that vitamin D deficiency may be a consequence rather than a cause of depression, as the association is stronger during summer when vitamin D status is influenced mostly by individual behavior and exposure to UVB radiation during outdoor activities.
However, the PHQ-9 may have a higher disciminative sensitivity in summertime given the generally higher levels of depressive symptoms and therefore smaller differences between 25(OH)D quartiles in wintertime. As the current study was a crossectional design and therefore precluding any causal implications, longitudinal studies considering the amount of activities in UVB exposure might help clarify the role of season in the association of vitamin D and depressive symptoms.

4.1 Limitations

Participants with severe depression or other severe diseases are likely to be underrepresented in the DEGS1 study sample. Furthermore, data on depressive symptoms and some of the covariables are based on self-reports. Regarding the association between vitamin D and depressive symptoms and its wide range of confounding factors, residual or unknown confounding cannot be excluded. Some confounders we did not control for, either because we

have not measured them at all or not comprehensively e.g. social support. For some important unmeasured confounders, we tried to include proxies in statistical models e.g. physical functioning and participation in sports activities for the amount of time spend outdoors and sunlight exposure.

Finally, although serum 25(OH)D is a commonly used biomarker of vitamin D status, there is no consensus in measurement due to a wide range of analytic methods, assays, and devices (Lips et al., 1999; Sempos et al., 2012). As reported in numerous studies, inter-assay differences can lead to dissimilar results for 25(OH)D (Binkley et al., 2004; Carter, 2012; Carter et al., 2004). The Liaison chemiluminescence immunoassay used in DEGS1, for example, tends to underestimate the concentration of 25(OH)D in the lower measurement range.

5. Conclusion

In conclusion, we found that current depressive symptoms defined by Patient Health Questionnaire (PHQ-9) were associated with vitamin D status in summer but not in wintertime in the adult population aged 18–79 years in Germany. The association in the summertime suggests that the relationship between vitamin D status and current depressive symptoms are greatest when UVB exposure opportunities are higher. These findings support the idea that vitamin D deficiency may be a consequence rather than a cause of depression. Longitudinal studies considering the amount of UVB exposure may help clarify the role of season in the association of vitamin D and depressive symptoms.

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Table 1. Characteristics of the study population (n=6.331) according to serum 25(OH)D quartiles and prevalence of elevated depressive symptoms (PHQ-9 >=10) *

	Total	**Serum 25(OH)D in nmol/l**					**Elevated depressive symptoms (PHQ-9 ≥=10)**		
	%	**Q1 (9-27)**	**Q2 (28-42)**	**Q3 (43-59)**	**Q4 (60-347)**	**p-value[1]**	**PHQ-9 <10**	**PHQ-9 >=10**	**p-value[1]**
		(n=1,512)	(n=1,578)	(n=1,569)	(n=1,672)		(n=5,892)	(n=439)	
Female sex	49.9	49.2	49.3	50.2	50.6	0.9	48.8	63.3	<0.001
Age group						<0.001			0.07
18-29 years	19.7	19.8	17.7	16.6	24.3		19.2	25.6	
30-39 years	15.0	16.7	14.0	12.6	16.3		14.9	15.6	
40-49 years	21.5	21.8	20.6	22.4	21.3		21.5	21.8	
50-59 years	18.7	18.6	20.6	19.9	16.2		18.8	17.8	
60-69 years	13.9	10.7	14.4	16.9	13.9		14.1	11.8	
70-79 years	11.2	12.4	12.7	11.8	8.1		11.5	7.3	
Summertime examination (May-October)	47.7	19.1	39.2	59.2	72.9	<0.001	47.5	50.2	0.4
Socio-economic status						<0.001			<0.001
Low	17.3	21.9	19.2	16.0	12.4		16.3	30.5	
Middle	61.5	60.1	60.4	60.5	64.7		61.9	56.7	
High	21.2	18.0	20.4	23.5	22.9		21.9	12.8	
Living in a partnership	79.9	74.6	80.4	81.9	82.6	<0.001	80.6	71.4	<0.001
Municipali						0.6			0.001

ty size								
<5.000 residents	15.8	14.9	16.2	17.0	15.3		16.1	12.7
5.000-<20.000 residents	24.1	20.2	24.0	24.9	27.2		24.7	16.6
20.000-<100.000 residents	29.0	30.3	27.9	28.8	28.9		28.7	31.8
>=100.000 residents	31.1	34.6	32.0	29.3	28.6		30.5	38.9
Country of birth						<0.001		0.005
Germany	87.7	85.0	89.0	87.4	89.2		88.3	79.7
Europe and Western countries	9.5	8.8	8.3	11.3	9.8		9.1	15.1
Arab-Islamic countries	2.1	5.2	1.6	0.7	0.8		1.9	4.3
Remaining countries	0.7	1.0	1.1	0.6	0.2		0.7	0.9

Table 1 (continued).

	Total	**Serum 25(OH)D in nmol/l**					
	%	**Q1 (9-27)**	**Q2 (28-42)**	**Q3 (43-59)**	**Q4 (60-347)**	**p-value[1]**	**P**
		(n=1,512)	(n=1,578)	(n=1,569)	(n=1,672)		(n=
Obesity (Body Mass Index >=30kg/m^2)	22.7	30.6	25.4	20.5	14.6	<0.001	
				Mean			
Physical Functioning Scale (SF-36), mean score	87.3	84.0	86.8	88.4	89.9	<0.001	
Mean eGFR in mL/min/1.73 m^2	95.3	97.6	93.7	93.4	96.5	<0.001	
No current smoking	70.5	67.3	70.8	75.7	68.5	0.001	
Alcohol consumption						<0.001	
no consumption	13.3	17.4	15.2	9.5	10.8		
<20g/day men, <10 g/day women	70.8	65.9	71.2	74.8	71.7		
>20g/day men, >10 g/day women	15.9	16.7	13.6	15.7	17.5		
Sport activity > 0 h/week	67.5	57.2	63.9	71.3	77.5	<0.001	

* Results are weighted population estimates expressed as column percentage unless otherwise indicated; abbreviations: Q = quartile; 25(OH)D = 25-hydroxy-vitamin D; PHQ-9 = Patient Health Questionnaire 9 item depression module; SF-36 = 36-Item Short Form Survey; eGFR = estimated glomerular filtration rate

[1] P-values are based on chi

[2] test for categorical variables and on linear regression for numerical variables; p-values refer to differences between groups according to 25(OH)D or elevated depressive symptoms in each sample characteristic

Table 2. Severity of depressive symptoms (mean PHQ-9 - score) and prevalence of elevated depressive symptoms (PHQ-9 >=10) according to vitamin D quartiles, year-round and stratified by half year

	Serum 25(OH)D in nmol/l				
	Q1	**Q2**	**Q3**	**Q4**	**p for trend**
PHQ-9 sum score, mean (95% CI)					
Year-round	4.47 (4.20-4.75)	3.96 (3.76-4.16)	3.94 (3.70-4.17)	3.90 (3.66-4.14)	0.002
Summer half year	5.32 (4.75-5.89)	4.18 (3.82-4.54)	3.90 (3.58-4.21)	3.83 (3.55-4.12)	<0.001
Winter half year	4.27 (3.97-4.57)	3.81 (3.58-4.05)	3.99 (3.64-4.35)	4.07 (3.61-4.53)	0.3
PHQ-9>=10, % (95% CI)					
Year-round	9.5 (7.6-11.8)	6.1 (4.8-7.8)	6.7 (5.2-8.6)	7.8 (6.1-9.8)	0.2
Summer half year	14.9 (10.4-20.9)	7.6 (5.3-10.7)	6.3 (4.4-9.0)	7.5 (5.6-10.0)	0.03
Winter half year	8.3 (6.3-10.8)	5.2 (3.6-7.3)	7.2 (5.0-10.2)	8.4 (5.5-12.7)	0.9

All figures are weighted population estimates.Abbreviations: Q = quartile; PHQ = Patient Health Questionnaire

Table 3. Results of multivariable linear regression analyses examining associations between 25(OH)D quartiles and severity of depressive symptoms (PHQ-9 score) stratified by extended seasons (November-April; May-October)

		Wintertime (November-April; n=3,263)				Summertime (May-October; n=3,068)			
		Beta	95 % CI		p-value	Beta	95 % CI		p-value
Model 1	Quartile 1	reference				reference			
	Quartile 2	-0.45	-0.81	-0.09	0.01	-1.03	-1.61	-0.44	<0.01
	Quartile 3	-0.25	-0.70	0.20	0.26	-1.32	-1.98	-0.66	<0.01
	Quartile 4	-0.32	-0.81	0.18	0.21	-1.46	-2.07	-0.86	<0.01
	trend	-0.11			0.17	-0.38			<0.01
Model 2	Quartile 1	reference				reference			
	Quartile 2	-0.37	-0.73	-0.01	0.05	-0.87	-1.45	-0.29	<0.01
	Quartile 3	-0.12	-0.58	0.34	0.61	-1.10	-1.73	-0.46	<0.01
	Quartile 4	-0.15	-0.66	0.36	0.56	-1.20	-1.81	-0.58	<0.01
	trend	-0.05			0.55	-0.30			<0.01
Model 3	Quartile 1	reference				reference			
	Quartile 2	-0.09	-0.42	0.25	0.61	-0.59	-1.19	0.02	0.06
	Quartile 3	0.23	-0.17	0.63	0.25	-0.63	-1.23	-0.02	0.04
	Quartile 4	0.20	-0.29	0.69	0.42	-0.72	-1.30	-0.14	0.02
	trend	0.09			0.25	-0.17			0.05
Model 4	Quartile 1	reference				reference			
	Quartile 2	-0.04	-0.38	0.29	0.80	-0.59	-1.19	0.02	0.06
	Quartile 3	0.29	-0.12	0.70	0.17	-0.62	-1.23	-0.02	0.04
	Quartile 4	0.22	-0.27	0.71	0.37	-0.73	-1.31	-0.14	0.02
	trend	0.10			0.20	-0.17			0.04

Abbreviations: 25(OH)D = 25-hydroxy-vitamin D; PHQ = Patient Health Questionnaire; CI = Confidence interval

Model 1: adjusted for sex and age

Model 2: Model 1 + adjusted for socio-economic status, partnership, municipality size and country of birth

Model 3: Model 2 + adjusted for obesity, physical functioning and eGFR

Model 4: Model 3 + adjusted for smoking status, alcohol consumption and sport activity

Table 4. Results of multivariable logistic regression analyses examining associations between 25(OH)D quartiles and elevated depressive symptoms (PHQ-9 >=10) stratified by extended season (November-April; May-October)

		Winter (November-April; n=3,263)				Summer (May-October; n=3,068)			
		OR	95 % CI		p-value	OR	95 % CI		p-value
Model 1	Quartile 1	reference				reference			
	Quartile 2	0.59	0.36	0.96	0.03	0.50	0.29	0.86	0.01
	Quartile 3	0.83	0.51	1.34	0.44	0.41	0.23	0.72	<0.01
	Quartile 4	0.91	0.56	1.49	0.71	0.47	0.27	0.79	0.01
	trend	0.96			0.59	0.82			0.03
Model 2	Quartile 1	reference				reference			
	Quartile 2	0.65	0.39	1.09	0.10	0.53	0.30	0.93	0.03
	Quartile 3	0.96	0.58	1.60	0.88	0.45	0.25	0.81	<0.01

	Quartile 4	1.10	0.67	1.79	0.71	0.55	0.32	0.97	0.04
	trend	1.02			0.77	0.87			0.13
Model 3	Quartile 1	reference				reference			
	Quartile 2	0.78	0.46	1.33	0.36	0.61	0.33	1.16	0.13
	Quartile 3	1.29	0.76	2.20	0.34	0.62	0.34	1.15	0.13
	Quartile 4	1.41	0.85	2.35	0.18	0.77	0.42	1.40	0.39
	trend	1.14			0.13	0.97			0.71
Model 4	Quartile 1	reference				reference			
	Quartile 2	0.83	0.49	1.40	0.48	0.61	0.32	1.16	0.13
	Quartile 3	1.41	0.84	2.37	0.20	0.65	0.36	1.19	0.16
	Quartile 4	1.50	0.91	2.47	0.11	0.79	0.44	1.44	0.44
	trend	1.17			0.07	0.98			0.81

Abbreviations: 25(OH)D = 25-hydroxy-vitamin D; PHQ = Patient Health Questionnaire; OR = Odds Ratio; CI = Confidence interval
Model 1: adjusted for sex and age
Model 2: Model 1 + adjusted for socio-economic status, partnership, municipality size and country of birth
Model 3: Model 2 + adjusted for obesity, physical functioning and eGFR
Model 4: Model 3 + adjusted for smoking status, alcohol consumption and sport activity

Highlights

- There are conflicting reports on the association between vitamin D and depression.
- Vitamin D status is associated with depressive symptoms only in summer time.
- Vitamin D deficiency may be a consequence rather than a cause of depression.